

Icatibant in hereditary angioedema: news and challenges

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Hereditary angioedema (HAE) is a rare condition. Its prognosis depends on whether there is laryngeal involvement with a risk of asphyxia, which is present in 25% of such cases. Improved understanding of the pathophysiology of this disease has resulted in the development of targeted therapies including icatibant, which acts as an antagonist at bradykinin B2 receptors. This agent has been shown to be effective in the treatment of attacks of HAE in three Phase III randomized double-blind published studies. Efficacy data have been collected in all types of attack: cutaneous, abdominal and laryngeal. Safety data are also encouraging. Icatibant is administered subcutaneously, with the potential for patients to self-administer. In the future, this therapy may offer increased independence for HAE patients.

KEYWORDS: bradykinin • hereditary angioedema • icatibant

Types I and II hereditary angioedema (HAE) are rare conditions with an estimated prevalence of between 1 in 100,000 and 1 in 50,000 [1,2]. They are associated with mutations of the *SERPINE1* gene causing a reduction in the production of C1-inhibitor protein (C1-Inh) or the production of an abnormal nonfunctioning protein [3]. They are characterized by recurrent episodes of oedema of the limbs, and the upper respiratory and digestive tracts, which can last for 48–96 h [4]. The prognosis is dependent on the laryngeal edema. The risk of death is estimated to be 25% if laryngeal edema is not treated with specific treatment [5]. These attacks are resistant to standard treatment for histaminergic angioedema such as corticosteroids and adrenaline. Involvement of the gastrointestinal system manifests as painful abdominal crises, often requiring treatment with opioid analgesics if not managed with specific therapy [6]. The unpredictable nature of suffering an attack can worsen the effects of the illness on the patient's quality of life. On average, a crisis results in 3.3 days loss of time from work [7]. Several effective therapies such as icatibant have emerged during the last 5 years.

Pathophysiology of HAE

Bradykinin is a nanopeptide. It is the most powerful native vasodilator [8] and is responsible

for increasing vascular permeability [9]. These biological effects are mediated via specific B2 receptors (coupled to protein G) carried on the surface of vascular endothelium and on smooth muscle [10]. Bradykinin is released from high-molecular-weight kininogen by the proteolytic action of kallikrein, which itself is a product of the splitting of prekallikrein by activated factor XII (FIGURE 1) [11]. C1-Inh partly controls this pathway by inhibiting factor XIIa and kallikrein. Bradykinin is rapidly metabolized by kininases, of which the angiotensin converting enzyme (ACE) is the major form. Thus, its half-life is less than 15 s [12].

In 1998, bradykinin was identified as the key mediator of HAE in man [13]. It was shown that its concentration increases during an attack of HAE, whereas it remains at normal concentration in cases of antihistamine responsive angioedema. The concentration then returns to normal between attacks [13]. In 2002 it was demonstrated that a specific B2 bradykinin receptor antagonist (icatibant) blocks vascular hyperpermeability in C1-Inh-deficient mice [14].

Drug treatment of HAE

Drug management of HAE has three aspects: the treatment of attacks, and long-term and short-term prophylaxis.

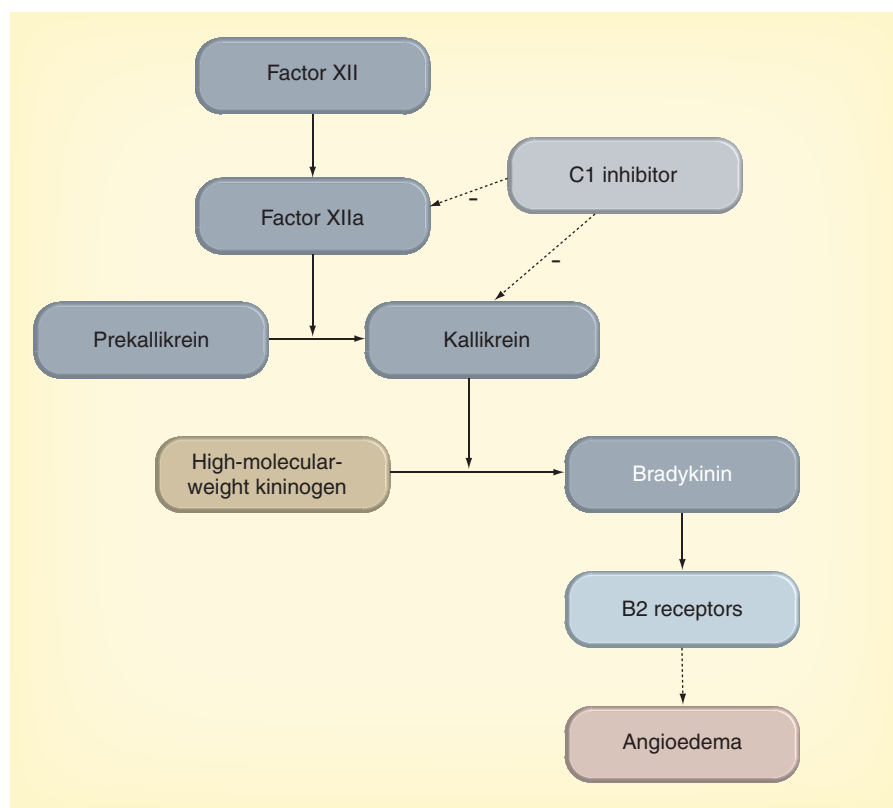


Figure 1. Kallikrein–kinin system.

Treatment of attacks

The international consensus states that any serious crisis must be treated with specific agents (C1-Inh concentrates, icatibant or ecallantide) [15]. This applies to attacks involving the face, the upper respiratory tract or the abdomen. The treatment should be administered as promptly as possible. Other attacks (cutaneous swelling other than face and neck) are either not treated or managed with antifibrinolytics. At present, there is no way of recognizing those patients at risk of having severe crises. Any patient is at risk even if he/she has never previously suffered a severe attack.

Long-term treatment

Long-term treatment is indicated when the patient has severe and frequent crises (more than once monthly), or where rapid access to treatment of an attack is not available. Three types of treatment may be recommended: antifibrinolytics, androgens and C1-Inh concentrate [15].

Short-term prophylaxis

If an urgent or major surgical procedure is to be carried out, then C1-Inh concentrate prophylaxis may be essential. With a minor planned procedure (such as mild dental work), prophylaxis with androgens is advised [15].

Pharmacology

Icatibant (HOE-140, JE-049) was characterized in 1990. It is a bradykinin analogue containing ten amino acids, five of which are synthetic and resistant to degradation [16,17]. It is a

highly selective competitive antagonist at the B2 receptor. Its affinity for the B2 receptor is similar to that of bradykinin with an IC_{50} of 1–10 nmol/l [18]. Its affinity for B1 receptors is much lower (<100 times) and no binding to other receptors has been reported thus far. Agonist activity is expressed at high concentrations (>3.2 mg/kg) and may explain the local reaction at the time of subcutaneous injection [19]. Icatibant's duration of action is not dose dependent, which is the reason why a second dose is preferable to an increase in dose when it has not been fully effective [20].

Icatibant is rapidly absorbed from the subcutaneous injection site: peak concentration is achieved in 30 min and bioavailability is high (96% for a dose of 0.4 mg/kg) [21]. Protein binding is weak (44%) and the distribution volume is large (20–25 l) [22]. The elimination half-life is 1.2–1.5 h [21]. Icatibant is broken down into two inactive metabolites, which are excreted in the urine. It has no effect on renal or hepatic function [22].

In vitro and animal experiments have demonstrated that icatibant lessens the

effects of bradykinin: reduction in both smooth muscle contraction and release of prostacyclin from endothelial cells, and diminution of bowel vascular permeability [16,17]. In healthy subjects it decreases bradykinin-induced vasodilatation, hypotension, reflex tachycardia and release of tissue plasminogen activator [23]. In a placebo-controlled Phase I study in healthy volunteers, the intravenous administration of icatibant inhibited the effects of intravenous injection of bradykinin in a dose- and time-dependent manner [24]. It is of interest to note that icatibant alone has no effect on the cardiovascular or rennin–angiotensin systems. However, it does inhibit the hypotensive effects of ACE inhibitors in healthy volunteers and hypertensive patients [25].

Clinical efficacy

Clinical effectiveness has been validated in an open study and in three double-blind randomized studies in patients with type I or II HAE.

A Phase II study (JE049-2101) has been carried out to estimate the optimal effective dose for treatment of an angioedematous crisis. A total of 20 attacks (in 15 patients) were treated either by 0.4 or 0.8 mg/kg of icatibant intravenously or by a 30- or 45-mg subcutaneous dose. The drug was effective for cutaneous and abdominal attacks over the 4 h following the injection. Efficacy was similar regardless of the route or dose of administration [26,27]. The 30-mg subcutaneous dose was, therefore, chosen for the Phase III studies.

The FAST-1 study was double blind and placebo controlled. It involved 56 patients (≥ 18 years of age) in the USA, Canada, Argentina and Australia [28]. FAST-2 was a double blind study against tranexamic acid (3 g per day for 2 days). This was performed in Europe and Israel in 74 patients (≥ 18 years of age) [28]. These studies involved all types of attack apart from laryngeal crises (TABLE 1), which were included in an open-label study. Both studies were followed by an open-label extension. The primary end point was the median time to clinically significant relief of symptoms defined by a minimum decrease of 30% in the index symptom score on the visual analogue scale (sustained for three consecutive measurements). One of the three main symptoms (cutaneous swelling, cutaneous pain and abdominal pain) was defined in each patient as the index symptom for the purpose of assessing the primary end point [28].

The primary end point was reached in 2.5 h with icatibant versus 4.6 h with placebo in the FAST-1 trial ($p = 0.14$) and in 2.0 versus 12.0 h with tranexamic acid in the FAST-2 study ($p < 0.001$). Differences in effectiveness between the two studies may be explained by several points of difference between them [28]:

- Study design: FAST-1 was mainly performed in the Americas, and compared icatibant to placebo. FAST-2 was carried out in Europe and evaluated icatibant against tranexamic acid;
- The type of attack treated: 51% of the crises in FAST-1 were abdominal, while this type accounted for only 36% of those studied in FAST-2;
- The method of treatment of crises in the control groups: patients could be treated symptomatically (i.e., with analgesics, anti-emetics, opiates or even C1-Inh concentrate). In FAST-1, 45% of the placebo group received treatment of this type compared with only 13% of patients in the tranexamic acid group (FAST-2) (TABLE 2). The inferior results in FAST-1 may, therefore, be explained by increased use of back-up treatment. Thus, with correction for data obtained in patients in whom there was recourse to symptomatic treatments, the results of FAST-1 become statistically significant (TABLE 3).

The median time to initial symptomatic improvement was significantly shorter with icatibant in FAST-1 and FAST-2 (TABLE 4). The time to almost complete relief of symptoms was significantly shorter with icatibant in FAST-2 (10 vs 51 h; $p < 0.001$) and shorter, but not statistically significantly so, in FAST-1 (8.5 vs 19.4 h; $p = 0.08$) [28].

A total of 11 patients received open-label icatibant for laryngeal symptoms. The median time to first improvement was 0.6–1.0 h and nine of the 11 patients had no symptoms at 4 h after icatibant administration.

Injection-site reactions were reported by the majority of patients in each study treated with icatibant (96–97%). Drug-related adverse events were reported by nine patients with icatibant (abnormal results on a liver function test in one patient, dizziness in one patient, nasal congestion in one patient, abdominal pain, nausea and worsening of an acute attack of angioedema in one patient, asthenia in one patient, injection-site reactions in

Table 1. Characteristics of the study patients in the FAST-1 and -2 trials.

Characteristic	FAST-1		FAST-2	
	Icatibant (n = 27)	Placebo (n = 29)	Icatibant (n = 36)	Tranexamic acid (n = 38)
Age (years)	34.8 $\pm$ 9.8	34.9 $\pm$ 11.4	40.4 $\pm$ 13.6	41.9 $\pm$ 12.4
Female/male	16/11	21/8	24/12	23/15
Cutaneous attacks	14	13	24	23
Abdominal attacks	13	16	12	15
Data from [28].				

two patients, two episodes of rash in one patient and one patient presented with worsening of an attack). No serious adverse event related to icatibant was reported.

The results of these studies led to European marketing authorization for icatibant in the treatment of attacks of HAE in adults (in 2008); US FDA approval has not yet been granted. A further study was, therefore, initiated (FAST-3) to obtain additional data on efficacy [101]. FAST-3 is a randomized, double-blind, placebo-controlled study using the same design as FAST-1. The results have not yet been published. A study (EASSI – Evaluation of the Safety of Self-Administration with Icatibant) to validate auto-administration of the drug at the time of an attack has been completed recently [102]. The results are expected to be known soon.

Potential developments

There are many types of bradykinin-mediated angioedema. In addition to type I and II HAE (associated with C1-Inh deficiency), there are type III HAE (no C1-Inh deficiency), acquired angioedema with C1-Inh deficiency (with or without anti-C1-Inh antibodies), and angioedema associated with ACE inhibitors or with angiotensin II antagonists [29]. The FAST studies were carried out in patients with hereditary C1-Inh deficiency. Up to now, there has been no prospective study for the use of icatibant in treating patients with other types of angioedema. The mechanism of action of icatibant and the pathophysiology of these conditions led one to believe that this treatment could be effective in treating attacks of other forms of bradykinin-mediated angioedema. Several published case reports are in favor of this hypothesis.

Table 2. Number of patients (%) who received rescue medication.

Time period	FAST-1		FAST-2	
	Icatibant	Placebo	Icatibant	Tranexamic acid
In the first 12 h	11	45	0	13
In the first 48 h	22	52	17	29
Data from [28].				

Table 3. Median time to onset of symptom relief (primary end point) adjusting or not for rescue medication.

Median time to onset of symptom relief	FAST-1			FAST-2		
	Icatibant	Placebo	p-value	Icatibant	Tranexamic acid	p-value
Primary end point (h)	2.5	4.6	0.14	2.0	12.0	<0.001
Primary end point adjusting for rescue medication (h)	2.5	9.0	0.02	2.0	16.0	<0.001
Data from [28].						

A positive response to icatibant was reported in three patients with acquired C1-Inh deficiency [30–32]. Zanichelli *et al.* reported the case of a man who responded poorly to C1-Inh concentrate. Icatibant was effective in five attacks involving the face and one laryngeal crisis [32].

The efficacy of icatibant in angioedemas associated with ACE inhibitors has been demonstrated by Bas *et al.* [33]. Eight patients received icatibant for edema of the tongue or larynx associated with enalapril or ramipril medication. The first symptomatic improvement after icatibant administration occurred at a mean of 50.6 min and symptoms had abated completely at 4.4 h (neither tracheotomy or intubation was performed). In the authors' historical comparison group, treated with methylprednisolone and clemastine, the mean time to complete relief of symptoms was 33 h and three patients received a tracheotomy while two were intubated [33].

Bouillet *et al.* reported good results with icatibant in three patients with type III HAE. The time to improvement of symptoms was between 1 and 2 h [34].

Conclusion

Improvements in the understanding of the pathophysiology of HAE have led to the development of novel therapeutic agents including icatibant. This specific treatment has the advantage that it can be administered by the subcutaneous route. This method of delivery means that self-administration is possible, which may offer increased patient independence. Thus patients may have more rapid access to effective treatment, regardless of geographic location. Safety data have been encouraging up to now but will need to be monitored as the drug is more widely prescribed. A surveillance provision, Icatibant Outcome Survey for Hereditary Angioedema (IOS), has recently been established and should ensure that this monitoring is carried out.

Expert commentary

Treatment of HAE has changed dramatically during the last 2 years. Five new drugs were tested in Phase III studies. The positive results allowed the market authorization in the USA for ecallantide (kallikrein inhibitor), C1-Inh concentrate (Berinert® [CSL Behring], Ceter [Sanquin]/Cinryze® [Viropharma]) and in Europe for icatibant,

C1-Inh recombinant and C1-Inh concentrate (Berinert, Ceter/Cinryze). All these drugs are indicated for attack treatment. Cinryze is only licensed for long-term prophylaxis. Icatibant may be an attractive option because of the subcutaneous injection and the possibility of self-injection. While direct comparative trials of icatibant versus alternative therapies have not been conducted, efficacy data appears to be generally comparable. Safety data have been encouraging up to now. In our center, we have trained 45 patients for self-adminis-

tration. A total of 19 patients have each experienced one to 14 acute HAE attacks (abdominal, laryngeal and facial) treated with icatibant. A total of 15 patients (79%) chose to self-administer icatibant. Symptoms improved rapidly following icatibant self-administration. Patients appreciated the prompt availability of treatment and the efficacy and safety of self-treatment [BOUILLET L, BOCCON-GIBOD I. UNPUBLISHED DATA].

Five-year view

Self-administration of icatibant is expected to be authorized in a few months. Therefore, training programs could be developed in others countries. By avoiding the need for hospital/emergency room admissions, self-administration may enhance patients' autonomy. However, some problems have to be considered: problems associated with incorrect injections, potential side effects, and medical and legal responsibility. In the future, we have to evaluate the indications of the different drugs (i.e., icatibant, ecallantide and C1-Inh concentrate) and their coadministration.

Financial & competing interests disclosure

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Table 4. Median time to first symptom improvement according to study group.

	FAST-1			FAST-2		
	Icatibant	Placebo	p-value	Icatibant	Tranexamic acid	p-value
Time to first symptom improvement according to patient	0.8	16.9	<0.001	0.8	7.9	<0.001
Time to first symptom improvement according to investigator	1.0	5.7	<0.001	1.5	6.9	<0.001
Data from [28].						

Key issues

- Hereditary angioedema (HAE) is associated with the risk of unpredictable life-threatening laryngeal edema.
- HAE attacks are resistant to treatment by corticosteroids and adrenaline, and require specific treatment.
- Icatibant, a bradykinin receptor antagonist, is effective for the treatment of all types of HAE attack.
- Self-administration of icatibant is possible because of the subcutaneous administration.

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